
NEUROLOGY OF LEARNING DISABILITIES: WHAT WILL THE FUTURE BRING? THE ANSWER COMES FROM THE SUCCESSES OF THE RECENT PAST

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My involvement with learning disabilities (LD) began approximately 25 years ago, at a time when formal research training was uncommon for medical doctors, and the apprenticeship model was the way most of us began our research careers. Of all the topics I had heard Norman Geschwind – at that time my neurology chairman and mentor – speak about, language held particular fascination for me, perhaps because of my own experience with having to learn and become competitive in a new language at age 15. After completing my residency, I began to work on anatomic brain asymmetries in an attempt to further understand the biological specialization of the left hemisphere for many aspects of language function. Then, Geschwind invited Friedrich Sanides, a late student of Oskar and Cecile Vogt (Brodmann was an earlier student), to travel to Boston from West Germany and spend a year here teaching me about cytoarchitectonics as a neuroanatomical tool to deepen the study of brain asymmetries. This took place in 1977.

In 1978, Geschwind suggested that I take over a project begun by Dr. Brooke Seckel, a resident two years my senior, who had decided to change careers (I often wondered whether it was the project that did it). It concerned the study of a brain from an individual with developmental dyslexia who had died as a result of a fall down an elevator shaft. His brain had become part of the Yakovlev Collection at the Boston City Hospital, where all of this took place. Brooke had been testing the hypothesis, advanced by Geschwind, that the brain of a dyslexic would show two small *plana temporale*. In 1968 Geschwind and his then student Walter Levitsky

had shown in the general population that the *planum temporale*, comprising part of the auditory association cortex involved in linguistic functions, was large on the left and small on the right, perhaps explaining language lateralization to the left hemisphere. Some normal brains showed the reverse asymmetry, and still others showed lack of asymmetry, with a large planum on both sides. It made sense to Geschwind, a believer in the phrenological principles that had been launched at the start of the nineteenth century, that in a condition with poor language function, the *plana* would be bilaterally small (in one interpretation of phrenology, more brain tissue means more function). Here is where I became involved.

As it turned out, the *plana temporale* were not small in the dyslexic brain, but were shown to be large in several specimens of dyslexic brains; later, additional alterations in planum asymmetry were reported. Animal experiments showed that under some conditions symmetry in a cortical area could be a response to a disorder of neuronal migration. In fact, the first dyslexic brain and many other brains showed cortical dysplasias and ectopias resulting from abnormal neuronal migration to the cerebral cortex during mid-gestation.

This finding began a productive area of research that lasted the better part of two decades. Initially, it was important to establish that these focal cortical malformations significantly disrupted cortico-cortical organization and cortico-thalamic interactions, to explain linguistic deficits, which was done after it was possible to model the anomalies in experimental rodent models. Second, it was necessary to show that the cortical mal-

formations and the cortico-thalamic anomalies produced (and were not simply correlated with) functional deficits. Thus, it was shown that induction of cortical malformations in the rat, similar to those found in the dyslexic brain, produced a variety of cognitive deficits, and that disturbances in cortico-thalamic networks were associated with perceptual deficits involving processing of rapidly changing sound stimuli. Thus, a causal interaction was established between focal disorders of neuronal migration and some behaviors that mimicked deficits found in populations of dyslexic individuals.

A second focus of research concerned the origin of the cortical and thalamic malformations in the dyslexic brain. A variety of sources were considered. Initially, immunological damage to the developing cortex was thought to be an etiologic factor because of an epidemiological study published by Geschwind and his colleague in Glasgow, Peter Behan, showing a link between immunological disorders, left-handedness, and dyslexia. However, sufficient support for this hypothesis was not obtained, but it has been found since then that cytokines may indeed modulate the cortical injury that leads to neuronal migration defects.

Hormonal effects were sought, too, since a sex difference in dyslexia was widely believed to exist, and sex steroids are known to modulate immunological function and are suspected to modulate cerebral lateralization. It was discovered that the male hormone testosterone was capable of modifying the thalamic plasticity that resulted from early cortical injury that led to neuronal migration defects. Male rats responded maladaptively to cortical injury, developing changes in the thalamus and deficits in auditory temporal processing, while females were eminently resistant. Immunomodulators such as IL-9 enlarged the size of the damage in males, but not in females. These observations were compatible with the findings of male predominant sex ratios in most studies looking at the prevalence of dyslexia.

Ultimately, it became clear from population genetics studies that the main precursors of dyslexia were abnormal genes. A number of susceptibility loci on several distinct human chromosomes have been reported, and more recently a susceptibility gene, *DYX1C1* (aka *EKN1*), was described first in a Finnish kindred (see Taipale et al., 2004). This same locus failed to associate in two other populations (from the United Kingdom and Canada), although an additional single nucleotide polymorphism within one of the *DYX1C1* introns did associate significantly with dyslexia in the Canadian population (see Wiggs et al., 2004, and Scerri et al., 2004). Ongoing research from our laboratories seems to indicate that this dyslexia susceptibility gene is part of a

molecular pathway for the migration of young neurons to the cerebral cortex, the interference with which leads to neuronal migration disorders comparable to those seen in dyslexic brains. There is preliminary evidence that at least another susceptibility gene on chromosome 6 may work this way, too.

Dyslexia may represent the first example of a LD whereby a possible pathway may link the observed behavior to an underlying neurological substrate that has a neurodevelopmental history beginning with an abnormal gene. Similar efforts are being made to link other cognitive disorders of development to a molecular pathway involved in brain development. The objective is to disclose a developmental brain pathway leading to a brain that has a particular structure and physiology, a set of perceptual, cognitive, and metacognitive associations, and a behavior explained by these cognitive structures and processes. Environments and learning are apt to play their respective roles, but their full impact can only be understood in terms of the brain they impinge upon.

THE FUTURE

So, what is in store for the future? A tentative pathway now exists between a gene mutation (of *DYX1C1*), abnormal cortical and thalamic development, and an auditory behavior that comprises at least one of the dyslexia behavioral phenotypes. However, several candidate loci need further clarification. What is the contribution to dyslexia of genes on susceptibility loci on chromosomes 1-3, 6, 11, 15, 18 and the X chromosome, among others, that may eventually be found to associate with dyslexia? I predict that genes will be discovered at these chromosomal loci that will have neuronal migration effects similar to those of *DYX1C1*, either because they work along the same pathway or in other neuronal migration pathways. If the latter, it will be found that variability in the dyslexia phenotype will be explained by the specific pathway that is affected. Additional work is needed to specify the plasticity mechanisms relating genetic mutations, cortical development, and secondary changes in the brain modulated by immune modulators and hormones, as well as other factors not yet identified.

Additional work is also needed to further characterize the behavioral phenotype in dyslexia. The exact nature of the phonological defect in dyslexia is not yet known. The exact developmental interaction between general and linguistic auditory processing needs be worked out. Other, non-phonological components may be identified as important explanatory mechanisms. The contribution of the visual system remains speculative. The role of the cerebellum remains circumstantial. Advances in neuroimaging research, including functional imaging

and the new tract tracing techniques, will link specific behavioral phenotypes to areas of abnormal activation and, hopefully, specific mutations. Finally, improved classification on the basis of identified gene mutations, brain activation patterns, and behavioral phenotypes will trigger the design and testing of specific therapies implemented at earlier and earlier stages of development, with the promise of much improved success for the expression of each child's full potential.

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